

WHAT IS CLAIMED IS:

- 1. A method for identifying inhibitors of neuronal degeneration comprising (a) cotransfecting eukaryotic host cells expressing a presentilin protein (PS), with a polynucleotide encoding a Par-4 polypeptide, and an NF-κB dependent reporter construct, (b) exposing the cotransfected cells to a candidate molecule, and (c) monitoring the ability of said candidate molecule to induce NF-κB activation.
- 2. The method of claim 1 wherein said eukaryotic host cells are mammalian cells endogenously expressing PS.
- 3. The method of claim 1 wherein said eukaryotic host cells are mammalian cells transfected with nucleic acid encoding PS.

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- 4. The method of claim 3 wherein said PS is PS1.
- -5. The method of claim 4 wherein said PS1 is human.
- 6. The method of claim 3 wherein said PS is FAD PS.
- . 7. The method of claim 6 wherein said FAD PS is FAD PS1.

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- . 8. The method of claim 7 wherein said FAD PS1 is human.
- 9. The method of claim 1 wherein said eukaryotic host cells are neuronal cells.
- 10. The method of claim 9 wherein said neuronal cells are cerebellar granule cells.
- 11. The method of claim 9 wherein said neuronal cells are organotypic brain cells obtained from transgenic mice genetically engineered to express human PS1.

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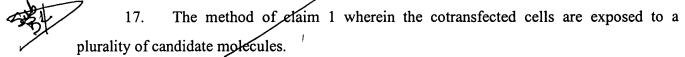
- 12. The method of claim 11 wherein said human PS1 is FAD PS1.
- 13. The method of claim 1 wherein said NF-κB dependent reporter construct comprises a luciferase reporter gene.
- 14. The method of claim 13 wherein said NF-κB dependent reporter construct comprises NF-κB-binding consensus sites linked to a luciferase reporter gene.
- 15. The method of claim 1 wherein the ability of said candidate molecule to induce NF-κB activation is monitored in comparison with a known inducer of NF-κB activation.
 - 16. The method of claim 15 wherein said known inducer of NF- κ B activation is TNF- α .

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- 18. The method of claim 1 further comprising the step of administering an identified inhibitor to a patient suffering from or at risk of acquiring a neurodegenerative disease.
- 19. The method of claim 18 wherein said neurodegenerative disease is Alzheimer's disease.
- 20. A method for identifying inhibitors of neuronal degeneration, comprising (a) transfecting eukaryotic host cells endogenously expressing Par-4 and a presentilin (PS) protein with nucleic acid encoding an NF-κB dependent reporter construct, (b) exposing the transfected cells to a candidate molecule, and (c) monitoring the ability of said candidate molecule to induce NF-κB activation
 - 21. The method of claim 20 wherein said eukaryotic host cells are HeLa cells.
- 22. The method of claim 20 wherein the transfected cells are exposed to a plurality of candidate molecules.
- 23. A method for identifying inhibitors of Par-4 expression or activity comprising (a) transfecting eukaryotic host cells endogenously expressing Par-4 and a presenilin (PS) protein with nucleic acid encoding an NF-κB dependent reporter construct, (b) exposing the transfected cells to a candidate molecule, and (c) monitoring the ability of said candidate molecule to induce NF-κB activation.
- 24. A method for identifying inhibitors of Par-4 expression or activity comprising (a) transfecting mammalian cells with nucleic acid comprising a Par-4 promoter region fused to a reporter gene, (b) exposing said cells to a pro-apoptotic agent followed by exposure to a candidate molecule, and (c) monitoring the ability of said candidate molecule to inhibit the activity of said reporter gene.
 - 25. The method of claim 24 wherein said Par-4 gene is of human origin.
 - 26. The method of claim 24 wherein said reporter gene is a luciferase gene.
- 27. The method of claim 24 wherein said cell is a cell line endogenously expressing Par-4.
 - 28. The method of claim 27 wherein said cell line is a HeLa cell line.

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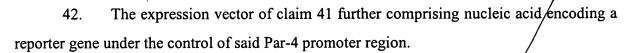
- 29. The method of claim 24 wherein said cell is exposed to a plurality of candidate molecules.
- 30. A method for identifying inhibitors of neuronal degeneration, comprising (a) exposing eukaryotic host cells expressing presentilin (PS) and Par-4 to a candidate molecule, and (b) monitoring the NF-kB DNA binding activity in the cell extract.
- 31. The method of claim 30 wherein NF-kB DNA binding activity is monitored by electrophoretic mobility shift assay.
- 32. A method for identifying inhibitors of neuronal degeneration, comprising (a) exposing eukaryotic host cells expressing presenilin (PS) and Par-4 to a candidate molecule, and (b) monitoring ξPKC in the cell extract.
- 33. The method of claim 32 wherein said ξPKC is monitored by an enzymatic assay.
- 34. A method for identifying inhibitors of neuronal degeneration, comprising (a) exposing eukaryotic host cells expressing presentilin (PS) and Par-4 to a candidate molecule, and (b) monitoring the level of IkB kinase (IKK) phosphorylation.
- 35. The method of claim \$4 wherein the level of IkB kinase (IKK) phosphorylation is measured by metabolic labeling and immunoprecipitation.
- 36. The method of claim 35 wherein immunoprecipitation of the cell extract is performed with IKK specific antibodies.
- 20 37. A method for identifying inhibitors of neuronal degeneration comprising (a) transfecting a mammalian cell with nucleic acid comprising a Par-4 promoter region fused to a reporter gene, (b) exposing said cell to a pro-apoptotic agent followed by exposure to a candidate molecule, and (c) monitoring the ability of said molecule to inhibit the activity of said reporter gene.
 - An isolated nucleic acid molecule comprising a Par-4 promoter region.
 - 39. / The nucleic acid molecule of claim 38 wherein said Par-4 is of human origin.
 - 40. An expression vector comprising a Par-4 promoter region.
 - 41. The expression vector of claim 40 further comprising nucleic acid encoding a heterologous polypeptide under the control of said Par-4 promoter region.

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- 43. The expression vector of claim 42 wherein said reporter gene is a luciferase gene.
- 44. A recombinant host cell transformed with an expression vector comprising nucleic acid encoding a heterologous polypeptide under the control of a Par-4 promoter region.
- 45. A method for producing a heterologous polypeptide comprising transforming a host cell with nucleic acid comprising the coding sequence of said polypeptide under control of a Par-4 promoter region and culturing the transformed host cell.
- 46. A method for identifying inhibitors of neuronal degeneration comprising (a) exposing eukaryotic host cells expressing presenilin (PS) and Par-4 to a candidate molecule, (b) exposing said cell to a pro-apoptotic agent, and (c) monitoring ξPKC in the cell extract.
- 47. The method of claim 46 wherein said ξPKC is monitored by an enzymatic assay.
- 48. A method of inhibiting Par-4 activity in eukaryotic cells comprising introducing into said cells a nucleic acid comprising a Par-4 promoter region.
- 49. A method of preventing neuronal degeneration in a mammal comprising introducing into said mammal a nucleic acid comprising a Par-4 promoter region.
- 50. A method of preventing neuronal degeneration in a mammal comprising introducing into said mammal an antisense nucleic acid comprising a sequence complementary to a Par-4 promoter region.
 - 51. Inhibitors of neuronal degeneration identified by the method of any of claims 1, 20, 30, 32, 34,37 and 46.
- 25 52. A process for obtaining a compound for the treatment of neuronal degeneration in a mammal, said process comprising:

screening a plurality of compounds for their ability to inhibit Par-4 activity; and preparing a pharmaceutical composition comprising one or more of said compounds identified in the screening and a suitable pharmaceutically acceptable carrier.